Dopamine versus noradrenaline in septic shock

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REVIEW

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Abstract

Background

The 'Surviving Sepsis' Campaign guidelines recommend the use of dopamine or noradrenaline as the first vasopressor in septic shock. However, information that guides clinicians in choosing between dopamine and noradrenaline as the first vasopressor in patients with septic shock is limited.

Objective

This article presents a review of the literature regarding the use of dopamine versus noradrenaline in patients with septic shock.

Results

Two randomised controlled trials (RCT) and two large prospective cohort studies were analysed. RCT data showed dopamine was associated with increased arrhythmic events. One cohort study found dopamine was associated with higher 30-day mortality. The other cohort study found noradrenaline was associated with higher 28-day mortality.

Discussion

Data on the use of dopamine versus noradrenaline in patients with septic shock is limited. Following the recent SOAP II study, there is now strong evidence that the use of dopamine in septic shock is associated with significantly more cardiovascular adverse events, compared to noradrenaline.

Conclusion

Noradrenaline should be used as the initial vasopressor in septic shock to avoid the arrhythmic events associated with dopamine.

Key Words

Dopamine, noradrenaline, norepinephrine, sepsis, septic shock, vasopressor

Background

The 2008 'Surviving Sepsis Campaign International Guidelines' define severe sepsis as acute organ dysfunction (e.g. hypotension, decreased urine output and elevated creatinine) secondary to infection.[1] Septic shock is defined as severe sepsis with hypotension that is refractory to fluid resuscitation.[1] Septic shock needs to be recognised and treated immediately as it carries high mortality. To maintain adequate organ perfusion, the administration of a vasopressor is required. The Surviving Sepsis Campaign recommends either noradrenaline or dopamine as the first choice vasopressor agent to correct hypotension in septic shock.[1]

Dopamine is the precursor for noradrenaline in the sympathetic nervous system.[2] At doses of 1–2µg/kilogram/minute, it mainly acts on vascular dopamine-1 receptors causing selective vasodilatation. At doses between 5 and 10 µg/kilogram/minute, dopamine also acts on beta-1 adrenergic receptors in the heart to increase cardiac output by increasing stroke volume and heart rate; at doses above 10 µg/kilogram/minute, it mainly acts on vascular alpha-1 adrenoceptors to cause vasoconstriction, increasing the systemic vascular resistance.[3] The adverse effects of dopamine include the suppression of prolactin, thyroid stimulating hormone and luteinising hormone.[4] It was previously believed that low dose dopamine in critically ill patients was reno-protective by increasing renal blood flow. This has been

disproven by RCT data: low dose dopamine does not offer significant protection against renal failure compared to placebo.[5]

Endogenously, noradrenaline is released from the nerve terminal of post-ganglionic sympathetic neurons.[2] It acts on alpha-1 adrenoceptors to cause vasoconstriction.[2] It also has a weaker action on beta-1 adrenoceptors.[3] However, noradrenaline's action on beta-1 adrenoceptors is cancelled out by a reflex bradycardia in response to the increased blood pressure.[3] Therefore, overall, the heart rate remains unchanged. Compared to dopamine, noradrenaline causes less tachycardia, and less tachyarrhythmia.

In clinical practice, there is no clear guideline that recommends when dopamine versus noradrenaline should be used in septic shock. This prompted a literature review on the use of dopamine versus noradrenaline in septic shock.

Method/Search strategy

A literature search was conducted using MEDLINE (via an EBSCOhost® search platform; publication date: 1962–2010). The terms searched were 'shock', 'dopamine' and 'noradrenaline'. These topics were matched by MEDLINE to the medical subject headings (MeSH) terms 'shock', 'dopamine' and 'norepinephrine'. Forty-six results yielded from a combined search of 'shock', 'dopamine' and 'norepinephrine'. The inclusion criteria were: if the studies were large prospective cohort studies, RCTs or systematic meta-analyses, and written in English. The articles were excluded if they were case reports or case series, or written in a language other than English. Of these, four relevant studies were identified and included in the literature review: two were RCT and two were large prospective cohort studies.

Results

RCTs

The Sepsis Occurrence in Acutely Ill Patients II (SOAP II) study was a multi-centre RCT that compared dopamine and noradrenaline as the initial vasopressor in the treatment of shock.[6] A total of 1,679 intensive care unit (ICU) patients with shock were randomised for treatment with dopamine (n=858) or noradrenaline (n=821) (Table 1).[6] All patients older than 18 years of age who required a vasopressor for the treatment of shock were included. The exclusion criteria were:

- under 18 years of age;
- already received a vasopressor for more than four hours during shock;
- serious arrhythmia: e.g. rapid atrial fibrillation or ventricular tachycardia;
- brain dead.

The parameters of shock used in the study were:

- mean arterial pressure <70mmHg; or
- systolic blood pressure <100mmHg despite adequate fluids; and
- signs of tissue hypoperfusion, such as:
  - altered mental state;
  - mottled skin;
  - urine output <0.5mL/kg for one hour;
  - lactate>2mmol/litre.

The patients were classified according to the type of shock: septic shock (n=1044, 62.2%), cardiogenic shock (n=280, 16.7%) and hypovolaemic shock (n=263, 15.7%).

Study	*Evidence*	*Patient numbers*	*Outcome measures*	*Intervention*	*Results*
SOAP II study, 2010[6]	RCT	1679: 858 in dopamine group; 821 in noradrenaline group	First outcome measures: mortality at 28 days after randomisation Second outcome measures: number of days without organ support and adverse events	Either dopamine or noradrenaline as 1st line vasopressor	No significant difference in morality at 28 days Dopamine associated with more arrhythmic events
Patel et al., 2010[7]	RCT	252: 134 in dopamine group; 118 in noradrenaline group	First outcome measures: mortality at 28 days after randomisation Second outcome measures: organ dysfunction, hospital and ICU length of stay and adverse events	Either dopamine or noradrenaline as first line vasopressor	No significant difference in mortality at 28 days Dopamine associated with more arrhythmic events
SOAP study, 2006[8]	Cohort study	1058: 375 in dopamine group; 683 in non-dopamine group	ICU/hospital mortality rates and 30-day survival	Not applicable	Dopamine group had higher ICU and hospital mortality rates, diminished 30-day survival
SACiUCI study, 2009[9]	Cohort study	458: 50.5% received dopamine; 73% received noradrenaline	Hospital mortality rate and 28-day survival	Not applicable	Noradrenaline group had reduced 28-day survival

Table 1: Levels of evidence and summary of results of the studies analysed in the literature review

When blood pressure could not be maintained at the pre-specified maximal dose of vasopressor (20µg/kilogram/minute for dopamine; or 0.19µg/kilogram/minute for noradrenaline), open-label noradrenaline, adrenaline or vasopressin could be added. There was no significant difference in the death rate at 28 days (52.5% in the dopamine group; 48.5% in the

noradrenaline group; P=0.10). There were significantly more arrhythmic events in the dopamine group, mostly atrial fibrillation (24.1% versus 12.4% in the noradrenaline group; P<0.001). A subgroup analysis showed that dopamine increased mortality at 28 days in cardiogenic, but not septic or hypovolaemic shock, when compared to noradrenaline.

The study by Patel et al. 2010 was a single centre RCT with a similar study design to SOAP II.[7] It involved a smaller number of patients with septic shock (n=252); 134 out of 252 patients were randomised to dopamine, and 118 patients were randomised to noradrenaline. It found no significant difference in mortality at 28 days (50% in the dopamine group; 43% in the noradrenaline group; P=0.282). There was a significantly increased incidence of arrhythmia in the dopamine group (19.4% versus 3.4% in the noradrenaline group).

Cohort studies

The SOAP study was a multi-centre, cohort observational study investigating dopamine use on the outcome of shock.[8] A total of 1,058 patients with shock were studied, of which 462 patients had septic shock. This cohort came from 3,147 ICU patients. All patients older than 15 years were included in the study. Those who stayed in the ICU less than 24 hours for routine post-operative observations and patients with burns were excluded. Patients were followed up until death, until hospital discharge, or for 60 days. Patients in the dopamine group were found to have higher ICU (42.9% versus 35.7%; P=0.2) and hospital (49.9% versus 41.7%, P=0.01) mortality rates.

The Sepsis Adquirida na Comunidade e internada em Unidade de Cuidados Intensivos (SACiUCI) study was also a multi-centre, cohort observational study.[9] A total of 897 consecutive patients admitted to ICU with community-acquired sepsis were studied; 458 patients had septic shock. All patients 18 years of age or older were included. They were followed up until death or hospital discharge. A total of 73% of patients received noradrenaline, compared to 50.5% for dopamine. Noradrenaline was associated with higher hospital mortality and diminished 28-day survival.

Discussion

Both RCTs had consistent findings: the rate of death at 28 days was not significantly different between dopamine and noradrenaline, but dopamine was associated with increased arrhythmic events.[6,7] The observational studies drew conflicting conclusions. The SOAP study concluded dopamine was associated with higher mortality at 30 days, while the SACiUCI study found noradrenaline was associated with higher mortality at 28 days.[8,9] The strength of the data from the observational studies is weaker because of the lack of randomisation. While a significant mortality difference between dopamine and noradrenaline was not demonstrated, it is important to note that an intention-to-treat analysis was used in the SOAP II study in 2010. This might underestimate any mortality difference between dopamine and noradrenaline. Of note, dopamine use in cardiogenic shock increased mortality, compared to noradrenaline.[6]

Taken together, the bulk of the data from the literature (SOAP II study 2010, Patel et al. study 2010) suggests that dopamine is associated with increased arrhythmic events compared to noradrenaline, and may even be associated with increased mortality.[8] Therefore, it could be argued that noradrenaline is the preferred first line vasopressor in septic shock. This data challenges the current guideline recommendation that dopamine should be one of the two first line vasopressor agents in septic shock.

Conclusion

The available data suggests that there is no significant difference in mortality at 28 days between patients treated with dopamine or noradrenaline as the first line vasopressor in septic shock. However, results from a small number of studies indicate that dopamine is associated with more arrhythmic events. Therefore, noradrenaline may be preferred over dopamine as the first line vasopressor in septic shock to avoid the adverse cardiovascular events.

Summary of important points

1. There is no significant mortality difference at 28 days in patients with septic shock treated with dopamine or noradrenaline.
2. Dopamine is associated with more arrhythmic events.
3. Noradrenaline might be preferred over dopamine as the first line vasopressor to avoid cardiovascular adverse events.
4. The recent SOAP II study challenges the guideline recommendation that dopamine should be one of two first line vasopressor agents in septic shock.

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CONFLICTS OF INTEREST

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